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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,768	09/24/2003	Yuqiao Shen	ONYX1047-DIV	8135

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 06/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/669,768	SHEN ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-19 and 23-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 , 13-19 and 23-32* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 4/5/06. Claims 1-10 and 20-22 have been cancelled. Claims 23-32 have been added. Claims 11-19 have been amended. Claims 11-19 and 23-32 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group V in the reply filed on 4/5/06 is acknowledged. The traversal is on the ground(s) that claim 11 and 14 represent a genus of claims drawn to rAd comprising mutated E1B-55K proteins comprising a single amino-acid mutation. The viruses have previously been found allowable. Upon reconsideration Groups V and VI have been rejoined. Therefore, claims 11-19 and 23-32 are under examination in this office action.

Priority

In the reference to the prior application inserted, as the first sentence of the specification of this application, the current status of all nonprovisional parent applications referenced should be updated. Specifically, U.S. Serial No. 09/918,696, filed 7/30/01, is now U.S. Patent No. 6, 635244, which is not indicated in the priority statement.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: the signatures of the inventors are so light that they are not legible.

Information Disclosure Statement

An IDS filed 4/5/06 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Drawings

Figure 3 is objected to under 37 CFR 1.83(a) because it fail to show any details as described in the specification. Specifically, figure 3 is a photograph of immunofluorescent cells. However, the details are indiscernible as the image is too dark. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 11 and 14 are objected to because of the following informalities: the claim recites that the ability of an E1B-55K mutated protein to bind to p53 is reduced when compared to the wild-type E1b-055K protein. For grammatical accuracy, it would be remedial to recite "when compared to the ability of wild-type E1B-55K protein to bind to p53".

Claim 11 is objected to for recitation of "said E1B-55K mutated protein", for accuracy, it would be remedial to recite -- said mutated E1B-55K protein --.

As well, claims 11 and 14 are objected to ass recitation of "said treatment" should be

-- the treatment -- for accuracy.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-19, 23 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation that the patient is administered "a polynucleotide sequence encoding a recombinant adenovirus" has been added to claim 14 and that the polynucleotide is RNA has

been added to claim 15. Applicant has indicated that support for this limitation is found throughout the specification as well as original claim 1. However, the examiner has been unable to find literal support in the originally filed specification or claims for the administration of "a polynucleotide sequence encoding a recombinant adenovirus". The specification does not contemplate administration of the polynucleotide encoding rAd for treatment but teaches infection of patients for delivery of the rAd. Therefore, the limitation is impermissible NEW MATTER.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 13-19 and 23-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration of a replication competent rAd to a tumor, does not reasonably provide enablement for treating any type of cancer in a human using a recombinant adenovirus comprising a single amino acid mutation in the E1B-55K gene and any other embodiments than replication competent using any other embodiments of administration than direct administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The instant invention is drawn to recombinant adenovirus comprising single amino acid mutations in the E1B-55K gene such that binding to p53 is reduced as compared to binding between p53 and wild-type E1B-55K. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention**. Applicants' claims are broadly drawn to treatment of any cancer using recombinant adenovirus comprising any mutation in E1B-55K in which the adenovirus comprises a single amino acid mutation in E1B-55K such that binding to p53 is reduced. Applicants' disclosure teaches development of two such mutants in which amino acid 240 and 260 are mutated to generate Onyx 051 and Onyx 053. These mutants are not able to bind to p53. As described in the specification, the method of the instant invention is directed toward treating cancer using the vectors and is based upon oncolytic replication function of the viruses in infected tumor cells.

3) **Number of working examples and guidance**. The instant invention is drawn to single amino acid mutations within E1B-55k that affect binding to p53. Applicants have constructed 26 mutant rAd in which a single amino acid within the E1B-55K coding sequence

was mutated (see e.g. page 12, ¶ 4 and table 2). Two of these mutant R240A and H260A lost ability to bind p53 but did not lose late viral function. Furthermore, the cells were tested for oncolytic affect. U20S and Du145 cells were assayed and demonstrated that the two viruses were cytotoxic.

4) **State of Art**. Enormous efforts have been directed toward the development of vectors for cancer treatments. Each goal alone is complex and requires great skill in the art. Adenovirus mutants that lack the ability to bind to p53 are replication deficient in non-replicating, non-neoplastic cells with p53 but in cells deficient in p53, the virus is replicative and oncolytic. Previously, the art has described generation of rAd comprising deletions, substitutions and frame-shifts which inactivate the ability of E1B-55K to bind to p53 efficiently to generate E1B-p53- mutants. For example, ad2 dl1520 (Onyx 015) comprises a frame-shift mutation at nucleotide position 2022 that generates a stop codon 3 amino acids downstream of the AUG codon resulting in deletion of large region of E1B, US patent 5,677,178 describes the generation of rAd lacking E4orf6 and US 6,080,578 teaches construction of Onyx 019, 020 and 021 in which various amounts of internal sequences are deleted.

5) **Unpredictability of the art**. The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the

instant case, there are multiple inoperative embodiments when considering the use of the instant invention in humans such as 1) the claims recite broadly treatment of all cancers however, the efficacy of oncolytic viruses based upon E1B mutations has not been demonstrated to be efficacious against any type of cancer and 2) the lack of recited route of administration of the rAd exacerbate the unpredictability of the art. In light of the art at the time of filing, the instant invention would require undue experimentation to perform the invention in humans.

The instant invention is unpredictable for treatment of cancer in humans for the following reasons. First, applicants' invention is based upon the premise that the targeted mutations within E1B-55K resulting a virus that is selective to tumor cells as tumor cells lack p53 while normal cells do not. The specification teaches that "Therapy of disease, preferably neoplastic disease, wherein the disease arises from loss of p53 or a defect in the p53 pathway, may be afforded by administering to a patient a composition comprising adenoviral E1B55K mutants of the invention." Kirn et al teach that "the role of p53 in replication-selectivity of dl1520 has been difficult to confirm despite extensive *in vitro* experimentation by many groups, E1B-55K gene deletion was associated with decreased replication and cytopathogenicity in p53(+) tumor cells versus matched p53(-) tumor cells, relative to wild-type in RKO and H1299 cells" (page 6653, col 1, ¶ 3). Therefore, the efficacy of the instant adenovirus lies in treatment of p53 (-) tumors. This efficacy has been specifically observed when in combination with chemotherapy (see Kirn et al, page 6666, col 1). Secondly, this premise is distinctly connected to the replicative condition of the rAd. However, by recitation that the rAd comprises an E1B-55K mutation, the adenovirus to be used in the treatment encompasses a broad and diverse genus of adenoviruses

that need only be linked by a mutation in E1B-55K. The nature of the adenoviruses for treatment of cancer according to the instant invention must be replicative.

Thirdly, the method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al (Verma and Somia, Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. Russell teaches "it should first be capable of gaining access to a sufficient number of tumour cells in the patient to bring about a desired therapeutic outcome. Reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle position in a tumour deposit." (page 1165, col 2, ¶ 4-5). In the instant case, the method of delivery of an Onyx based virus is problematic, intratumoral injection is the preferred route of administration as it limits the virus to target tissue due to its cytotoxicity Adenoviral vector use for gene therapy is hindered by the transient nature of the transgene expression coupled with host immune responses. Attempts through oncolytic viral therapy to capitalize on the cell-killing or cellular immune response are also thwarted by the humoral immune responses as taught by Verma and Somia; "Unfortunately for gene therapy, most of the human population will probably have antibodies to adenovirus from previous infection with the naturally occurring virus" (Verma and Somia, p 241). And "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less

desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene (p. 4, column 2).

6) **Summary**. The invention recites a method for treatment of cancer using a replicative adenovirus vector. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established protocols and the inability to predict successful administration of the rAd: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Conclusion

Claims 11, 13-19 and 23-32 are rejected.

Claim 12 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1633

June 7, 2006

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER